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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
12/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/604,984	BENTWICH, ITZHAK	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,44 and 50-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,44 and 50-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/11/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Specification

The application contains disclosure entirely outside the bounds of the claims. Applicant is required to modify the brief summary of the invention and restrict the descriptive matter so as to be in harmony with the claims (MPEP § 1302.01).

Double Patenting

Claims 21, 44 and 50-53 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 8, 11 and 12 of copending Application No. 10/605,838. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are directed to SEQ ID NOs: 4641 and 4642, disclosed by the instant specification as a bioinformatically detectable gene. The claims of the '838 application are directed to bioinformatically detectable gene sequences having the structural limitations of the instant claims. Therefore, the instant claims are a species of and would anticipate the generic claims of the '838 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant requests that the obviousness-type double patenting rejection be withdrawn pursuant to MPEP § 804.I.B1 because the instant application predates the filing date of the '838 application.

This portion of the MPEP states that a provisional obviousness-type double patenting rejection should be withdrawn in an earlier-filed application when it is the only rejection remaining. Because this is not the only rejection against the instant claims, the provisional rejection is maintained.

Double Patenting-New

Claims 21, 44 and 50-53 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21, 27, 33 ,34, 35, 41, 47 and 48 of copending Application No. 10/536,560. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are directed to SEQ ID NOs: 4641 and 4642, disclosed by the instant specification as bioinformatically detectable genes having homology with Epstein-Barr, a DNA virus, and SEQ ID NOs: 1916 and 1917, disclosed by the instant specification as precursors that encode SEQ ID NOs: 4641 and 4642. The instant specification further discloses that these sequences are viral sequences. The claims of the '560 application are directed to viral nucleic acids having the structural limitations of the instant claims. Therefore, the instant claims are a species of and would anticipate the generic claims of the '560 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 101 & § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21, 44 and 50-53 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well established utility.

The claims are directed to isolated nucleic acids consisting of SEQ ID NOs: 4641 and 4642 and their complements, as well as SEQ ID NOs: 1916 and 1917, disclosed in the instant specification as precursor molecules encoding SEQ ID NOs: 4641 and 4642. The claims are further directed to vectors and probes comprising these sequences.

A review of the specification finds general assertions and statements that the invention relates to a group of bioinformatically detectable novel genes, referred to as "viral genomic address messenger" or "VGAM" genes, which are believed to be related to micro RNAs (miRNAs); short ~22nt non-coding regulatory RNA oligonucleotides that are found in a wide range of species and believed to function as specific gene repressors. The specification makes general statements that VGAMs and the miRNAs

they may encode may have utility for regulating target genes and possibly for treating viral infection.

The specification discloses that VGAMs are novel, non-protein coding, viral regulatory genes that represent precursor miRNAs or miRNA-like sequences encoded by a virus genome. Such sequences are predicted to have a hairpin like structure and to give rise to short, ~22-nt RNAs, which presumably provide gene repression activity like that of known miRNAs.

However, the specification provides no direct or indirect evidence for any credible utility of RNAs encoded by the instantly claimed SEQ ID NOs: 1916 or 1917. There is no disclosure suggesting that SEQ ID NOs: 4641 or 4642 have ever been isolated or prepared or studied or examined under any conditions. Any asserted utility for the claimed sequences appears to be merely speculation based on "bioinformatics," homology, and secondary structure predictions suggesting that the claimed RNAs are miRNAs because they have a miRNA-like hairpin structure and some degree of sequence homology to some target sequence. Applicant's asserted utility appears to be based only on the predicted structure and sequence complementarity of sequences meeting the criteria of VGAM sequences and on various reports in the prior art describing various genes and their correlation to diseases. From this, applicant appears to extrapolate and thereby assert that inhibiting or somehow altering a target gene is beneficial, and that because the claimed sequences have a predicted miRNA-like precursor structure and a sequence that is complementarity to some target sequence, they play a role in inhibiting a target gene and treating a disease.

There is no evidence of record that the nucleic acid sequences encompassed by the claims play any role in disease. It appears that SEQ ID NOs: 1916 and 1917 are part of the genome of Epstein-Barr virus, but there is no indication that these SEQ ID NOs are actually processed into miRNAs having the sequences identified as SEQ ID NOs: 4641 and 4642. While the claimed sequences may have complementarity to a gene, applicant has not presented any evidence or established any nexus that SEQ ID NOs: 4641 or 4642 target and/or inhibit a specific gene, much less that the expression or inhibition of expression of these sequences may be used to prevent or treat a disease associated with a target sequence.

Applicant has not shown, and there is no evidence in the prior art to suggest, that the nucleic acids now claimed are expressed in any cell whatsoever. Indeed, the asserted utility and target gene of this and thousands of other miRNA-like sequences appears to be based purely on bioinformatic methods for predicting RNA folding and potential gene targets.

Krutzfeldt et al. (Nature Genetics 2006) state that, in general, the basis for these types of prediction programs is the degree of sequence complementarity between a miRNA and a target UTR, including the presence of a consecutive string of base pairs at the 5' end of the miRNA known as a 'seed' or 'nucleus', and the cross-species conservation of this binding site. On average, 200 genes are predicted to be regulated by a single miRNA. They further state that reviewing the data provided by these algorithms determining candidate targets uncovers the entire gamut of gene categories, such as transcription factors, protein kinases, vesicular trafficking molecules and

membrane receptors, suggesting that there is no apparent bias towards one particular function.

Those in the art additionally recognize that prediction of miRNAs yields many predicted miRNAs that have no biological function. For example, John et al. (PLoS Biology 2004) reports prediction of miRNA targets using an algorithm based on several factors including sequence complementarity between miRNA and target site and evolutionary conservation of the target sequence (see page 1864, second paragraph). The authors commit most of pages 1864-6 and Table S8 of their summary article to explaining their methods of validating predicted miRNA targets, specifically noting that "only a small number of target sites of target genes regulated by miRNAs have been experimentally verified," (page 1864, last paragraph). At page 1865 in the sixth paragraph, the authors report that the percentage of false positives for target transcripts with more than two, three, and four sites is 39%, 30%, and 24%, respectively, and that the false-positive rate for single sites is about 35%. Furthermore, the authors indicate that the usefulness of their prediction method is to facilitate focused experiments (abstract) and to facilitate evaluation of the predictions (page 1864, fifth paragraph). Thus, although miRNA target predictions were accomplished, the real-life value of each predicted miRNA needed to be assessed by experimentation.

Accordingly, while the ability to predict hairpin-like structures and potential gene targets from genomic sequence information appears to be within the state of the art, the art also teaches that validating the true biological function of any predicted miRNA sequence requires analyzing miRNA expression patterns, as well as testing the effects

of miRNA overexpression and underexpression under different conditions in living cells *in vitro* and *in vivo*. While these methods are within the level of skill in the art, applicant has presented no evidence that these validation techniques have been carried out with regard to the instantly claimed sequences. That is, no evidence can be found verifying or even suggesting that the sequences encompassed by the claims actually give rise to miRNAs in any cell or organism, and if they do, applicant has not described or shown any specific, substantial, or credible utility for the expressed miRNA. The fact that a miRNA can regulate gene expression is not a specific or substantial utility because this activity is inherent to almost any miRNA.

Based on the teachings in the art, any sequences predicted by an algorithm require validation. Without disclosure in the specification of a credible utility for the claimed SEQ ID NOs, one of skill would be left to *de novo* screening testing to identify such function, with no assurance that any practical or beneficial function would ever be identified. There is no evidence to suggest the nucleic acid sequences of the instant invention would provide any real world information for a specific use other than general knowledge as to understanding the biological function of the miRNA and they therefore lack credible utility.

Claims 21, 44 and 50-53 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Response to Arguments

Applicant traverses the rejection by arguing that, in contrast to *In re Fisher*, the instant application states that each of the disclosed nucleic acids may be used to target and modulate expression of gene transcripts and state that the instantly claimed sequences are disclosed as targeting COL6A1. Based on these arguments applicant asserts that the claimed sequences have a specific utility.

This is unpersuasive because while the specification postulates that the claimed sequences will modulate COL6A1, neither the art nor the specification provides evidence that such modulation occurs and those in the art recognize (based on the teachings of John et al.) that sequences predicted by algorithms require experimental validation.

Applicant further argues that the claimed sequences have a substantial utility because they may be used to bind and regulate mRNA transcripts of COL6A1, a subunit of extracellular matrix protein collagen VI, mutants of which are involved in Bethlem myopathy.

This is not persuasive because as stated above the specific utility asserted for the instant sequences is only hypothetical, therefore even if modulation of COL6A1 does provide a benefit to the public, applicant has not shown that the claimed sequences can actually provide this benefit.

Applicant argues that the claimed sequences have a credible utility, citing experimental evidence (provided as an appendix to the remarks) that the claimed Epstein-Barr Virus-related nucleic acids regulate the asserted target COL6A1.

The data discussed in the remarks is not considered to be objective factual evidence because it is not presented in the form of a declaration and therefore is considered to be an argument by applicant's counsel, which cannot take the place of evidence (see MPEP 716.01(c)).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

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